REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated June 1, 2006 are respectfully requested.

I. Amendment to the Specification

The specification is amended to remove reference to embedded hyperlinks in paragraph beginning on page 18, line 22, as requested by the Examiner. No new matter is added by this amendment.

II. Rejections under 35 U.S.C. §103(a)

Claims 1-5, 11 and 12 were rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Hellstrom et al., Mather and Hubbell et al.

Claim 6 was rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Hellstrom et al., Mather and Hubbell et al., and further in view of Houston et al.

Claims 7, 8 and 13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al., Mather and Hubbell et al., and further in view of Deftos et al.

Claim 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al., Mather, Hubbell et al. and Deftos et al., and further in view of Papahadjopoulos et al.

Claim 10 was rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al., Mather and Hubbell et al., and further in view of Forney et al.

These rejections are respectfully traversed in view of the following remarks.

A. The claimed invention

The present invention, as embodied in claim 1, is directed to a pharmaceutical composition for use in inhibiting growth of cancer cells in a mammalian subject. The composition comprises a urease enzyme, and associated with the enzyme, a chemical entity effective to enhance the delivery of the enzyme to cancer cells, when the composition is administered to the subject.

B. The Cited Art

HELLSTROM ET AL. disclose a monoclonal antibody that is specific for a tumor-associated antigen. Column 1, lines 28-34 note that the antibody may serve as a target-specific carrier of one of a variety of anti-tumor agent, including enzymes, for use in therapy. Nowhere does the patent disclose or suggest the enzyme urease as an anti-tumor compound to which the antibody of the invention may be conjugated.

MATHER discloses an antibody that binds to an antigen CD46 present on a variety of human cancer cells. The patent discloses, at paragraph 0135, that the antibody may be conjugated to a therapeutic compound, or to liposomes or other vesicles containing a therapeutic compound, to target the compound to cancer cells containing the antigen. Nowhere does the patent disclose or suggest urease (or any other enzyme) as an anti-tumor compound to which the antibody of the invention may be conjugated.

HUBBELL ET AL.is concerned with materials that can be polymerized under mild conditions to form gels capable of encapsulating biological materials, such as cells and tissues. One application of the gels, as set out in column 16, lines 1-16, is for "Entrapment of enzymes for correction of metabolic disorders and chemotherapy" (column 16, lines 1-2.) The paragraph following this heading (column 16, lines 3-16) reads:

> There are many diseases and defects which result from a deficiency in enzymes. For example, congenital deficiency of the enzyme catalase causes acatalasemia. Immobilization of catalase in PEG gel networks could provide a method of enzyme replacement to treat this disease. Entrapment of glucosidase can similarly be useful in treating Gaucher's disease. Microspherical PEG gels entrapping urease can be used in extracorporeal blood to convert urea into ammonia. Enzymes such as asparaginase can degrade amino acids needed by tumor cells. Immunogenicity of these enzymes prevents direct use for chemotherapy. Entrapment of such enzymes in immunoprotective PEG gels, however, can support successful chemotherapy. A suitable formulation can be designed for either slow release or no release of the enzyme.

The Examiner has read this paragraph as suggesting the use of urease for chemotherapy, based on the following logic: "Hubbel et al., at column 16 lines 15, discuss entrapment of enzyme for chemotherapy. They first discuss enzymes including urease and then state "immunogenicity of these enzymes prevents direct use for chemotherapy." Entrapment of such enzymes in immunoprotective gels, however, can support successful chemotherapy."

With all due respect, the interpretation of this passage given by the Examiner is unsupported by any reasonable reading. As noted above, the passage in question is subtitled (in column 16, lines 1-2): "Entrapment of Enzymes for Correction of Metabolic Disorders and Chemotherapy," clearly intending two distinct applications. The portion of the passage dealing with Metabolic Disorders, in which urease is discussed," is in lines 3-10 of the column 16. The portion of the passage dealing with chemotherapy, which makes no mention of urease, is in lines 11-16 of column 16.

Further to this point, the portion of the passage in lines 3-10 give three examples of enzymes that may be used in treating metabolic disorders: "For example, congenital deficiency of the enzyme catalase causes acatalasemia. Immobilization of catalase in PEG gel networks could provide a method of enzyme replacement to treat this disease. Entrapment of glucosidase can similarly be useful in treating Gaucher's disease. Microspherical PEG gels entrapping urease can be used in extracorporeal blood to convert urea into ammonia." All three of the enzymes and conditions noted in the passage are directed to correcting a metabolic disorder and none, as far as the Applicants know, have anything to do with treating cancer. The specific use of urease is in removing urea from extracorporeal blood, presumably during dialysis, by converting the urea to ammonia, which could then be removed in gas phase.

Further, the portion of the passage concerned with chemotherapy (lines 11-16 in column 16) notes that "enzymes such as asparaginase can degrade amino acids needed for tumor cells," but that "Immunogenicity of these enzymes prevents direct us in chemotherapy." Since the only use of urease suggested in the patent is for extracorporeal removal of urea from blood, immunogenicity of the enzyme would not be

an issue. That is, the rationale for encapsulating a chemotherapeutic enzyme would not even apply to the suggested use of and rationale for encapsulating urease.

4. Houston et al. is concerned with coil-coil leucine-zipper structures for forming two-subunit peptide compositions. The reference nowhere shows or suggests a urease/targeting composition for treating cancer.

5. Deftos et al. is directed to a liposome calcitonin composition, and more generally, with liposomes as carriers of therapeutic agents. The reference nowhere shows or suggests a urease/targeting composition for treating cancer.

6. Paphadjopoulos et al discloses conjugating liposomes with targeting agents, for targeting the liposomes to a suitable target site. The reference nowhere shows or suggests a urease/targeting composition for treating cancer.

7. Forney et al. is cited for its teaching of regulation of proteases with protease inhibitors. The reference nowhere shows or suggests a urease/targeting composition for treating cancer.

C. Analysis

According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

1. Rejection over Hellstrom et al., Mather and Hubbell et al.

Hubbell does not show or suggest using urease to treat cancer, for the reasons noted above. The only use of urease proposed in the reference for converting urea to ammonia is in extracorporeal blood (blood outside the body), presumably for dialysis or other extracorporeal applications. With respect to the Examiner's suggestion that a gel-coated enzyme be targeted with a tissue-specific antibody, it is not clear whether and how an antibody could be attached to a gel particle to target the particle, and whether

such a gel-particle composition would even be able to reach a target site, or be effective at the target site.

None of the other references cited by the Examiner disclose or suggest a composition for treating cancer that includes the enzyme urease, and thus would not make up the deficiencies in Hubbell et al.

Because none of the references, taken alone or in combination, shows or suggests the invention of claim 1, the standard for obviousness as applied to this claim, has not been met. Claims 2-13, which depend from claim 1, patentably define over the cited art for the same reason that claim 1 does. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

In view of the foregoing, Applicants submit that the claims pending in the application are in condition for Allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4401.

Respectfully submitted,

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